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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,306	02/12/2002	Jan Urban Kristoffer Hellstrand	MAXIM.026C3	1217

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EXAMINER	
HOLLERAN, ANNE L	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,306	HELLSTRAND ET AL.	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/7/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed 1/7/2005 is acknowledged. Claims 1-16 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

Priority

3. The amendment of the specification to add the phrase "now U.S. Patent No. 6,375,946" in paragraph 0001 is acknowledged.

Information Disclosure Statement

4. The courtesy copies of missing references are acknowledged and the references have been considered. A signed PTO-1449 is included with this Office action.

Double Patenting

5. The rejection of claims 1-16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2 and 11 of U.S. Patent No. 6,071,509 (previously incorrectly identified as 6,071,501) is withdrawn in view of the terminal disclaimer.

6. The rejection of claims 1-16 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2 and 11 of U.S. Patent No. 6,375,946 is withdrawn in view of the terminal disclaimer.

7. The rejection of claims 1-8 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,063,373 is withdrawn in view of the terminal disclaimer.

8. The rejection of claims 1-8 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,245,563 is withdrawn in view of the terminal disclaimer.

Claim Rejections - 35 USC § 112

9. The rejection of claims 1-16 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

10. The rejection of claims 1-16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn upon further consideration and in view of applicants' arguments.

New Grounds of Rejection:

11. Claims 8-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. The basis of this rejection is that the amendment to claim 8, adding the limitation "wherein said NK cell activating cytokine is not IL-2" is not supported by the specification or the claims as originally filed.

Applicants point to support for this amendment at paragraphs [0035] ad [0036]. However, these paragraphs do not teach the concept of a method for inhibiting tumor growth in a subject suffering from neoplastic disease comprising the step of administering an NK activating cytokine that is not IL-2 and further comprising administering an effective amount of a hydrogen peroxide scavenger. Paragraph [0035] teaches dosages range of IL-1, IL-2 and IL-12 for use in methods of treating neoplastic disease; and paragraph [0036] teaches dosage ranges of IFN-α, IFN-β and IFN-γ for use in methods of treating neoplastic disease. Therefore, neither of these paragraphs provides support for the negative limitation that defines a genus of NK cell activating cytokines that does not include IL-2. A review of the specification fails to demonstrate that support for such a negative limitation occurs elsewhere in the specification. Therefore, the amendment to claim 8 introduces new matter into the specification as originally filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 8-11 are rejected under 35 U.S.C. 102(e) as being anticipated by Paul (U.S. 5,626,883; issued May 6, 1997; effective filing date Apr. 15, 1994).

The claims are drawn to methods for inhibiting tumor growth in a subject suffering from neoplastic disease comprising administering to the subject an NK cell activating flavonoid; and also administering a hydrogen peroxide scavenger, which may be ascorbate. The administration may be simultaneous.

Paul teaches ascobate preparations that include flavonoids such as hesperidin, rutin, quercetin, proanthocyanidins, flavonols, and methoxyflavonols (see col. 7, line 60 to col. 8, line 3). Paul teaches methods of treating cancer by activating NK cells (col. 5, lines 36-62). Therefore, Paul teaches methods that are the same as that claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mark (U.S. Patent 4,588,585; issued 5/13/1986) in view of Hellstrand (Hellstrand, et al, Cellular Immunology 138: 44-54, 1991; cited in the IDS).

The claims are drawn to methods for inhibiting tumor growth in a subject suffering from neoplastic disease comprising administering to the subject an NK cell activating cytokine or NK cell activating flavonoid, wherein the NK cell activating cytokine is not IL-2 or IFN-α; and also

administering a compound selected from the group consisting of histamine, other H_2 receptor agonists and serotonin. The administration may be simultaneous, or may be separated in time by at most 24 hours. The dose of cytokine may be from about 1,000 to about 300,000 U/Kg/day. Claim 5 includes the dose range of flavonoids, but with respect to administering cytokines, the claim has the same scope as that of claim 1. The dose range of histamine, other H_2 agonist or serotonin if from aobut 0.1 to about 10 mg/day. The administration of cytokine or histamine, H_2 receptor agonist or serotonin may be administered parenterally to the patient.

Mark teaches a method of treating neoplasia by administering IFN-β mutein, and that the administration of IFN- β mutein is effective to activate natural killer cells (see col. 14, line 3 – col. 15, line 29; see also claims 8 and 10). Mark teaches a dosage range of 100,000 U to 400 million units (col. 14, lines 40-43), which encompasses the dosage range of the claimed inventions. Mark teaches administration of IFN- β mutein in combination with other therapeutic agents (col. 15, lines 5-6). Mark teaches parenteral administration of IFN- β mutein (col. 14, lines 66-67).

Mark fails to teach the specific combination of IFN- β mutein with a histamine, other H_2 agonist or serotonin. However, Hellstrand teaches that histamine reverses mono-induces down-modulation of NK- cells (see abstract) and that histamine augments anti-tumor cytotoxicity of NK cells (see page 45, 2nd full paragraph).

The methods of claims 1-5, 7 and 8 can be viewed as a methods drawn to administering a combination of ingredients known in the art to be useful for the same purpose, i.e. an In re Kerkhoven analysis (In re Kerkhoven, 626, F.2s 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)). The court held that it is obvious to combine two compositions, in order to form a third

composition, when each of the two compositions is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (MPEP 2144.06). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the IFN- β mutein of Mark and histamine as taught by Hellstrand, because the prior art teaches that both are useful for the treatment of tumors, and because the art teaches that both are useful for augmenting NK cell anti-tumor cell cytotoxicity.

With respect to the timing of administration (claims 2 and 3), where the administration may be simultaneous or separated in time by at most 24 hours, to the dose range of histamine, other H_2 agonist or serotonin (claim 6), it would have been well within the skill of one of ordinary skill in the art at the time the invention was made to have optimized the conditions of administration and dose range of histamine, other H_2 agonist or serotonin (see MPEP 2144.05).

14. Claims 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mark (U.S. Patent 4,588,585; issued 5/13/1986) in view of Paul (U.S. Patent 5,626,883; issued May 6, 1997; effective filing date Apr. 15, 1994).

Mark teaches a method of treating neoplasia by administering IFN-β mutein, and that the administration of IFN- β mutein is effective to activate natural killer cells (see col. 14, line 3 – col. 15, line 29; see also claims 8 and 10). Mark teaches a dosage range of 100,000 Units to 400 million Units (col. 14, lines 40-43), which encompasses the dosage range of the claimed inventions. Mark teaches administration of IFN- β mutein in combination with other therapeutic

agents (col. 15, lines 5-6). Mark teaches parenteral and oral administration of IFN- β mutein (col. 14, lines 66-67).

Mark fails to teach the specific combination of IFN- β mutein with a hydrogen peroxide scavenger. However, Paul teaches methods of administering a vitamin C supplement that comprises ascorbate (see abstract) for the purpose of enhancing the NK cell activity and treating cancer (col. 5, lines 36-62). Mark teaches vitamin C is thought to enhance activity of natural killer cells that spontaneously kill tumor cells (see col. 2, lines 57-67). Mark teaches methods of administering therapeutically beneficial amounts of ascorbic acid metabolites, which positively affect or enhance NK cell activity (col. 4, lines 31-49). Mark appears to teach that the vitamin C preparations may be administered orally, and fails to specifically teach that the vitamin C preparations may be administered parentarally.

The methods of claims 8-14 can be viewed as a methods drawn to administering a combination of ingredients known in the art to be useful for the same purpose, i.e. an In re Kerkhoven analysis (In re Kerkhoven, 626, F.2s 846, 850, 205 USPQ 1069, 1072 (CCPA 1980)). The court held that it is obvious to combine two compositions, in order to form a third composition, when each of the two compositions is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art (MPEP 2144.06). Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the IFN- β mutein of Mark and a vitamin C preparation as taught by Paul, because the prior art teaches that both are useful for the treatment of tumors, and because the art teaches that both are useful for augmenting NK cell anti-tumor cell cytotoxicity.

With respect to the timing of administration (claims 11 and 12), where the administration may be simultaneous or separated in time by at most 24 hours, it would have been well within the skill of one of ordinary skill in the art at the time the invention was made to have optimized the conditions of administration (see MPEP 2144.05).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
April 18, 2005

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER